REMARKS

Claims 1-16 are currently pending in the application. Claims 12-16 are canceled herein without prejudice as drawn to non-elected subject matter. Applicant reserves the right to prosecute the subject matter of these claims, and any unclaimed subject matter, in a related application. Claim 1 is amended to recite that both of the recited single-stranded fragments contain at least one mutation sequence. Claim 2 is amended the clarify which strands contains particular mutations. Support for these amendments is found at least in paragraphs 0017 and 0018 of the published application. Claims 8 and 9 are amended to recited that the polynucleotide encodes a YMDD site. Upon entry of the present amendments, claims 1-11 will be pending in this application.

It is submitted that no new matter has been introduced by the present amendments and entry of the same is respectfully requested.

Priority

Applicant submits herewith certified copies of Korean priority application nos. 10-2002-0063832 and 10-2003-0061066. As such, the effective priority date of the pending claims is October 18, 2002. Applicant respectfully requests that the Examiner enter these documents into the record and take note of the priority date.

The Rejections Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

The Examiner has rejected claims 8 and 9 under 35 U.S.C. § 112, second paragraph, as indefinite in that "it is unclear how the [recited] polynucleotide could comprise the amino acids of the YMDD site." Office Action, page 3. Applicant has amended claims 8 and 9 to recite that the polynucleotide comprises a polynucleotide sequence encoding the YMDD site. Thus, claims 8 and 9 as amended are sufficiently definite. Applicant therefore respectfully requests that the Examiner withdraw the rejections of claims 8 and 9 on this basis.

The Rejections Under 35 U.S.C. § 102(a) Should be Withdrawn

The Examiner has rejected claims 1-9 under 35 U.S.C. § 102(a) as allegedly anticipated by Kim *et al.*, *Korean J. Genetics* 25:63-75 (2003) ("Kim"). Office action at page 4. As noted above, Applicant submits with this Amendment certified copies of the two Korean priority applications. As such, the present application enjoys a priority date of October 18, 2002.

Because this date is earlier than the publication date of Kim, Kim is not available as a reference under § 102(a).

Applicant therefore respectfully requests that the Examiner withdraw the rejection of claims 1-9 on this basis.

The Rejections Under 35 U.S.C. § 103(a) Should be Withdrawn

The Examiner has rejected the claims under 35 U.S.C. § 103(a) as allegedly obvious over different combinations of references. Applicant traverses with respect to each combination of references below.

Rejection of Claims 1 and 2 Over Stanton

The Examiner has rejected claims 1 and 2 under 35 U.S.C. § 103(a) as allegedly obvious over Stanton *et al.* (WO 01/90419; "Stanton"). Office Action at pages 6-7. Without acceding to the Examiner's characterization of Stanton's teachings, Applicant has amended claim 1 herein to recite that, in step (b), *both* of the single-stranded fragments in the restriction fragment created by the recited restriction endonucleases comprise at least one mutation sequence. Claim 2 is amended herein to recite that all mutations within the restriction fragment are contained in one of the single-stranded fragments. Stanton consistently teaches either the generation of a single fragment or the generation of two fragments of 2-32 nucleotides, only one of which has the mutation sequence. *See, e.g.*, FIGS. 1-10. The advantage of creating two fragments each of which comprises the mutation sequence, not taught or suggested by Stanton, is that one can easily discern mispriming and amplification of an incorrect sequence where both single-stranded fragments comprise the mutation sequence. Stanton likewise does not teach or suggest the creation of a single-stranded fragment comprising more than one mutation, for example, all mutations contained within the restriction fragment, as recited in amended claim 2. As a result, Stanton does not teach or suggest the method of claims 1 and 2 as amended.

Applicant therefore respectfully requests that the Examiner withdraw the rejection of claim 1 and 2 on this basis.

Rejection of Claims 3-7 Over Stanton in View of New England Biolabs Catalog

The Examiner has rejected claims 3-7 under 35 U.S.C. § 103(a) as allegedly obvious over Stanton *et al.* (WO 01/90419; "Stanton") in view of the 2001-2002 New England Biolabs catalog ("NEB"). Office Action at pages 8-10. The Examiner states that Stanton does

not specifically teach cleaving a target with first and second restriction endonucleases under conditions in which the second endonuclease does not cleave, then under conditions in which the second endonucleases does cleave, or the use of first and second endonucleases that have different optimum temperatures. Office Action at page 9. The Examiner states, however, that Stanton teaches only that the only requirement for primer design is that the restriction enzyme sites generate fragments of the appropriate size, and comprise a polymorphic site, and that NEB teaches a table of restriction enzymes, including *Fok*I and *Bst*F51.

However, while Stanton ostensibly teaches that the restriction enzyme sites generate fragments of an appropriate size, Stanton does not teach the desirability of selecting two restriction enzymes that work optimally under different conditions, so that, for example, the restriction reaction by one endonuclease proceeds unhindered by the second endonuclease, particularly where the recognition sites for the two endonucleases overlap or are adjacent. The Examiner states that the motivation for combining Stanton with NEB is that "Stanton teaches that the only requirement for primer design is that the restriction enzyme sites used will generate fragment(s) of an appropriate size for mass spectrometry." Office Action at page 10. However, this is essentially an admission that Stanton provides *no* teaching as to the desirability of selecting two restriction endonucleases, one of which works under conditions in which the other does not. The NEB does not remedy this deficiency, because it teaches only a bare list of restriction endonucleases, and does not provide the teaching or suggestion of selection of the endonucleases based on reaction conditions, as recited in claims 3-7. For example, the combination of Stanton and NEB fails to teach or suggest the selection of a first restriction endonuclease from the group consisting of *Fok*1, *Bbv*I, *Bsg*I, *Bcg*I, *Bpm*I, *Bse*RI and *Bae*I, and a second restriction enzyme from the group consisting of *Bst*F5I, *Taq*I, *Bsa*BI, *Btr*I, *Bst*API, *Fau*I, *Bcl*I, *Pci*I and *Apo*I, as recited in claims 6 and 7, or why one would select one endonuclease from the first group and one from the second group, as opposed to two endonucleases from either the first or the second groups. As such, the combination of Stanton and NEB fails to teach or suggest the method of these claims.

Applicant therefore respectfully requests that the Examiner withdraw the rejection of claims 3-7 on this basis.

Rejection of Claims 1 and 8 Over Niesters in View of Stanton

The Examiner has rejected claims 1 and 8 under 35 U.S.C. § 103(a) as allegedly obvious over Niesters, *J. Med. Microbiol.* 51:695-699 (2002) in view of Stanton. Office Action as pages 11-13. The Examiner states that Niesters teaches a method of identifying a mutation in the YMDD motif of the DNA polymerase gene of hepatitis B virus (HBV) by PCR amplification and digestion with *Sfc*I, but that Niesters does not teach the use of two restriction endonucleases to identify the mutation. Office Action at page 11.

As noted above, Stanton does not teach or suggest each of the limitations of claim 1 as amended because Stanton does not teach the generation of fragments, each strand of which comprises the mutation sequence. Niesters does not remedy this omission, as it teaches only the generation of a double-stranded polynucleotide that is cleaved at the mutation site by a single restriction endonuclease. The combination of Niesters and Stanton, therefore, fails to teach or suggest every limitation of claim 1, or of claim 8, which depends from claim 1. Moreover, Niesters teaches the detection of only a single mutation, not a strategy for detecting any YMDD mutation in HBV. Neither Niesters nor Stanton teach or suggest the nucleotide sequence of HBV; a person of skill in the art would thus be forced to look outside these two references to identify, *e.g.*, appropriate restriction enzymes to use for a mutation in the YMDD site of hepatitis B virus.

There must be some teaching or motivation in the references themselves, or in the art, that would lead one of skill in the art to combine the references to obtain the claimed invention. Such motivation is lacking in the combination of Niesters and Stanton. Niesters teaches a relatively simple method for detecting a mutation, that requires only one restriction endonuclease and a simple agarose gel to determine whether or not the mutation is present. Niesters fails to teach that this method is deficient in any way. Stanton, in contrast, teaches a more complex method using two restriction endonucleases and a mass spectrometer to determine whether or not a mutation is present. Nothing in Stanton teaches or suggests that this more complex method is superior to the method taught in Niesters. Thus, there is no suggestion in the cited references to combine the references.

With respect to claim 8, Stanton states that the method disclosed therein is "applicable to genetic analysis of any diploid organism," and nowhere teaches the characterization of mutations in viruses. Stanton thus teaches away from the detection of a

mutation in a haploid viral genome. Stanton at page 39. Thus, a person of skill in the art would not be motivated to combine the cited references to analyze the particular hepatitis B virus mutation recited in pending claim 8.

Applicant therefore respectfully requests that the Examiner withdraw the rejection of claims 1 and 8 on this basis.

Rejection of Claims 3 and 9 Over Niesters, Stanton, and NEB

The Examiner has rejected claims 3 and 9 under 35 U.S.C. § 103(a) as allegedly obvious over Niesters in view of Stanton and NEB. Office action at pages 13-16.

As noted above, the combination of Stanton and NEB fails to teach or suggest the method of claim 3, at least because the references in combination do not teach or suggest the selection of two restriction endonucleases, one of which functions under conditions in which the other does not. Niesters, as noted above, teaches only the generation of a double-stranded polynucleotide that is cleaved at the mutation site by a single restriction endonuclease. The addition of Niesters to Stanton and NEB fails to teach or suggest the method of claim 3, as Niesters only teaches the detection of a specific HBV mutation, and does not teach the selection of the required two endonucleases, one of which functions under conditions in which the other does not. Because the cited combination of references does not teach or suggest the method of claim 3, the cited combination of references also does not teach or suggest the method of claim 9, which depends from claim 3.

Applicant therefore respectfully requests that the Examiner withdraw the rejection of claims 3 and 9 on this basis.

Rejection of Claims 1 and 10 Over Nguyen and Stanton

The Examiner has rejected claims 1 and 10 under 35 U.S.C. § 103(a) as allegedly obvious over Nguyen *et al., J. Med. Virol.* 54:20-25 (1998) ("Nguyen") in view of Stanton. Office Action at pages 17-19. As discussed above, Stanton does not teach or suggest the method of claim 1 as amended, at least because Stanton does not teach the creation of two single-stranded fragments, each of which contains at least one mutation sequence. Nguyen does not remedy this deficiency, as Nguyen teaches only the sequencing of an amplified sequence in the HCV 5′ region that contains a mutation. As such, the combination of Nguyen and Stanton does not teach or suggest all of the limitations of claim 1, or of claim 10, which depends from claim 1. Moreover, Nguyen states in the Abstract that "[d]ue to the presence of genotypes 4 and 5 found

in this panel of French patients (9.3%), HCV genotyping based on sequence determination is recommended," clearly teaching away from the invention of claims 1 and 10. Thus, a person of skill in the art would not be motivated to combine Nguyen and Stanton to obtain the method of claims 1 and 10.

Applicant therefore respectfully requests that the Examiner withdraw the rejection of claims 1 and 10 on this basis.

Rejection of Claims 3 and 11 Over Nguyen, Stanton and NEB

The Examiner has rejected claims 3 and 11 under 35 U.S.C. § 103(a) as allegedly obvious over Nguyen in view of Stanton and NEB. Office Action at pages 19-22. As explained above, the combination of Stanton and NEB fails to teach or suggest the method of claim 3, at least because that combination fails to teach or suggest the use of two restriction endonucleases, one of which works under conditions in which the other does not. Nguyen does not remedy this deficiency, as Nguyen teaches only the sequencing of an amplified sequence in the HCV 5' region that contains a mutation, and does not teach or suggest the use of two restriction endonucleases. As such, the combination of Nguyen, Stanton and NEB does not teach or suggest all of the limitations of claim 1, or of claim 10, which depends from claim 1. Moreover, Nguyen states in the Abstract that "[d]ue to the presence of genotypes 4 and 5 found in this panel of French patients (9.3%), HCV genotyping based on sequence determination is recommended," clearly teaching away from the invention of claims 3 and 11. Thus, a person of skill in the art would not be motivated to combine Nguyen and Stanton to obtain the method of claims 1 and 10.

Applicant therefore respectfully requests that the Examiner withdraw the rejection of claims 3 and 11 on this basis.

CONCLUSION

Applicant respectfully requests that the above amendments and remarks be entered in the present application file. An early allowance of the present application is respectfully requested. Should the Examiner have any concerns as to the allowability of any pending claim, or has concerns that any claim, as amended, would require further search, the Examiner is invited to contact the undersigned at 858-314-1171 or 858-314-1200 to discuss the matter to facilitate allowance of the application.

No fee, other than the extension of time fee, is believed due for this Amendment. However, if a fee is due, please charge such fee to Jones Day Deposit Account No. 50-2468.

Respectfully submitted,

Date: April 12, 2006

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